

Occlusive Mesenteric Ischemia in Chronic Dialysis Patients

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ABSTRACT **Background:** Among dialysis patients, occlusive mesenteric vascular disease has rarely been reported. **Objectives:** To report on the experience of one center with regard to diagnosing and treating this complication. **Methods:** The retrospective case-series involved six patients (3 females, 3 males; age 52–88 years; 5/6 were smokers) on chronic hemodialysis at a single center. All patients with symptoms suggestive of occlusive mesenteric disease and a subsequent angiographic intervention were included. Demographic, clinical, and laboratory data were collected from patient charts for the period before and after angioplasty and stenting of the mesenteric vessels. A Wilcoxon signed-rank test was used to compare the relevant data before and after the intervention. **Results:** All participants had variable co-morbidities and postprandial abdominal pain, food aversion, and weight loss. CT angiography was limited due to heavy vascular calcifications. All underwent angioplasty with stenting of the superior mesenteric artery (4 patients) or the celiac artery (2 patients). All procedures were successful in resolving abdominal pain, malnutrition, and inflammation. Weight loss before was 15 ± 2 kg and weight gain after was 6 ± 2 kg. C-reactive protein decreased from 13.4 ± 5.2 mg/dl to 2.2 ± 0.4 mg/dl ($P < 0.05$). Serum albumin increased from 3.0 ± 0.2 g/dl to 3.9 ± 0.1 g/dl ($P < 0.05$). Two patients underwent a repeat procedure (4 years, 5 months, respectively). Follow-up ranged from 0.5–7 years. **Conclusions:** Occlusive mesenteric ischemia occurs among dialysis patients. The diagnosis requires a high degree of suspicion, and it is manageable by angiography and stenting of the most involved mesenteric artery.

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KEY WORDS: abdominal angina, chronic kidney disease-5 (CKD-5), hemodialysis, mesenteric ischemia

Mesenteric ischemia among patients treated by chronic hemodialysis is usually non-occlusive in nature [1-3]. This highly fatal complication is often precipitated by intradialytic hypotension. It presents in an acute fashion and necessitates immediate diagnostic and therapeutic interventions.

Occlusive mesenteric vascular disease is different. It presents with chronic abdominal angina, with postprandial abdominal pain and weight loss or aversion to food. Diagnosis is often delayed, especially in hemodialysis patients, as the symptoms are often mistakenly related to peptic disease or malignancy [4-6]. Occlusive mesenteric vascular disease among dialysis patients has received only scant recognition in the past [7-10].

The incidence of occlusive mesenteric ischemia among dialysis patients is not known. One epidemiological study estimated its incidence at 2.7/1000 patient-years, a staggering incidence 44-fold higher when compared to the non-dialysis population [11]. However, a major limitation of that study was the inclusion of severe acute incidents leading to surgery without adequately differentiating between occlusive and non-occlusive disease. The mortality rate was high: 74% among the hemodialysis patients and similar to that described for non-occlusive events among dialysis patients [1,2]. Thus, it is possible that a large proportion of that cohort actually presented with non-occlusive mesenteric ischemia.

We have encountered six patients with mesenteric arterial occlusive disease among our chronic hemodialysis patients. All of these patients had severe and generalized atherosclerotic vascular disease. In this article, we present the experience of a single center in dealing with this condition. We found that early recognition using the correct radiological options led, in most cases, to successful angiographic therapy and improved survival.

PATIENTS AND METHODS

This retrospective case-series involved patients on chronic hemodialysis at a single center. Demographic, clinical and laboratory data were collected from patient charts for the period before and after angiographic interventions of the mesenteric vessels. The study was approved by the Rabin Medical Center Helsinki committee.

All patients underwent computed tomography angiography (CTA) or diagnostic angiography (if the true lumen was not clearly demonstrated because of heavy calcifications in the mesenteric arterial walls) to determine the involvement and the severity of the mesenteric vessels.

After receiving informed consent, we performed angiographies under local anesthesia via the femoral arteries (7 procedures) or trans-brachial (2 interventions in one patient because of chronic infrarenal aortic occlusion). The images were obtained in lateral projections to better demonstrate the mesenteric vessels origin. After verification of the severity of stenosis (greater than 80% at the origin of at least 2 mesenteric vessels), the most diseased vessel (celiac, or preferably the superior mesenteric artery [SMA] if both were at the same stenosis grade) was treated by primary stenting using balloon-mounted stents. Dynamic, or Racer bate metal stents (Biotronik, Berlin, Germany) were used in all. In two patients with in-stent re-stenosis balloon angioplasty was performed to achieve re-dilatation of the stenotic vessels.

Angiographic success was considered when the stenotic vessel was fully opened in the primary procedures and balloon dilatation of over 80% comparing to the non-stenotic adjacent vessel in the secondary interventions.

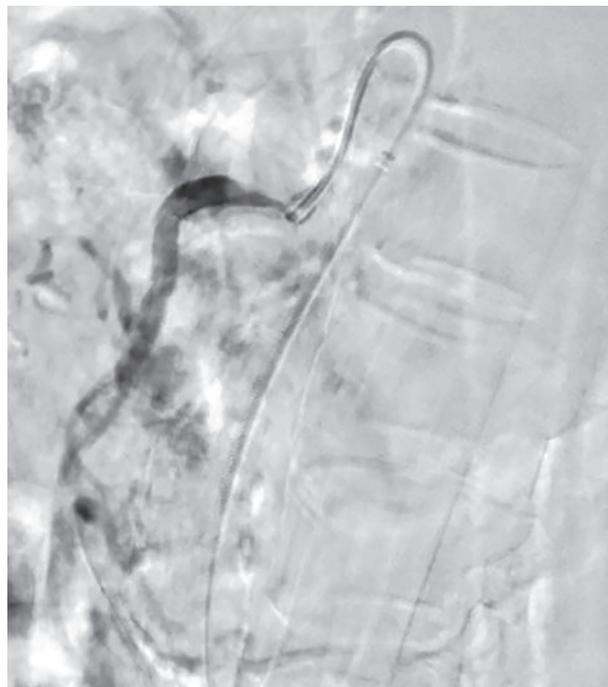
A representative image before and after stenting the SMA in one of the patients is shown in Figures 1-2.

Figure 1. Computed tomography post contrast sagittal reconstruction demonstrating calcified aorta and stenosis of the superior mesenteric artery origin



Figure 2. SMA angiography

[A] A tight SMA stenosis is verified by selective SMA angiography



[B] Completion angiogram after primary stent placement, verifying SMA patency; additional celiac artery stenosis is demonstrated
SMA = superior mesenteric artery



RESULTS

The study group included six patients, three males and three females, age 52–88 years. All patients had documented atherosclerotic vascular disease involving the coronary, carotid, and peripheral arteries. Three had renovascular disease. Five patients were smokers, two presented with diabetes mellitus. Five patients had been on hemodialysis for 2–11 years. One patient with chronic kidney disease-5 (CKD-5) initiated hemodialysis 8 months after the procedure.

The clinical and laboratory data before and after the therapeutic angiography are presented in Tables 1 and 2.

PATIENT 1

A 66-year-old female with autosomal dominant polycystic kidney disease (ADPKD) had been treated by hemodialysis for 11 years. She was a heavy smoker and presented with ischemic cardiomyopathy. Ten years into the dialysis treatment she started to complain of abdominal pain toward the end of the dialysis sessions. Non-occlusive mesenteric ischemia was suspected. An abdominal angiography showed a heavily calcified abdominal aorta, a severely calcified celiac trunk with a 50% proximal stenosis, and a calcified SMA with 50–60% peri-ostial stenosis. The inferior mesenteric artery was calcified, narrow but patent. Initial therapy consisted of keeping the patient slightly hyper-

Table 1. Patient characteristics

Patient	Age	Sex	Renal disease	Years on hemodialysis	Co-morbidities	Smoker	Year	Artery	Follow-up, years	Outcome
1	66	Female	ADPKD	11	IHD, DCM, Obesity	Yes	2006, 2010	SMA (2×)	5	Unrelated death
2	80	Male	Atherosclerosis, RAS	2	PVD, AF, COPD	Yes	2007	Celiac	4	Unrelated death
3	52	Male	DN	5	DM2, CABG, Obesity	Yes	2011	SMA	7	Unrelated death
4	60	Male	DN, atherosclerosis	3	DM2, CABG, AF, PVD	Yes	2012	SMA	2.5	Unrelated death
5	88	Female	UD	2	PVD, CVA, Dementia	No	2016	SMA	0.4	Unrelated death
6	60	Female	Atherosclerosis, RAS	pre- HD	PVD, APLA	Yes	2016	Celiac (2×)	2	Alive

ADPKD = autosomal dominant polycystic kidney disease, AF = atrial fibrillation, APLA = antiphospholipid antibody syndrome, CABG = coronary artery bypass graft, COPD = chronic obstructive pulmonary disease, CVA = cerebrovascular accident, DCM = dilated cardiomyopathy, DM2 = diabetes mellitus, DN = diabetic nephropathy, IHD = ischemic heart disease, PVD = peripheral vascular disease, RAS = renal artery stenosis, SMA = superior mesenteric artery, UD = undetermined

Table 2. Serum laboratory data and weight, before and after therapeutic interventions

Patient	Δ weight pre (kg)	Δ weight post (kg)	cRP* pre (mg/dl)	cRP post (mg/dl)	Albumin* pre (gr/dl)	Albumin post (gr/dl)
1	-20	+6	20.5	0.9	3.1	3.8
2	-17	na	35.0	3.1	2.7	4.0
3	-11	+11	3.2	1.9	3.5	4.0
4	na**	+6	8.2	2.6	3.6	4.2
5	na**	na	13.0	2.3	2.6	3.5
6	-12	+2	0.6	Na	2.7	4.1
mean±SE	-15±2	6±2	13.4±5.2	2.2±0.4***	3.0±0.2	3.9±0.1***

*Normal levels: CRP = 0-0.8 mg/dl (since mid-2014 = 0-0.5 mg/dl), albumin = 3.4-4.6 g/dl

**Changes in body weight could not be accurately evaluated since the patient was intentionally left hypervolemic to avoid events of mesenteric ischemia

***P < 0.05 by Wilcoxon signed-rank test

volemic to avoid hypotension and maintaining her pre-dialysis hemoglobin level at approximately 10 gr/dl, so as to avoid post-dialysis hemoconcentration. However, the patient continued to complain of worsening postprandial abdominal pain and lost 20 kg. The malnutrition-inflammation-atherosclerosis (MIA) syndrome became evident [Table 2] with hypoalbuminemia and elevated serum C-reactive protein (CRP). The degree of stenosis in the mesenteric vessels was hard to determine on CTA due to intravascular calcifications. A transfemoral angiography demonstrated progression of the proximal SMA stenosis to approximately 80%, and a 60–70% narrowing of the celiac trunk. A stent was placed in the SMA. This procedure was followed by a significant clinical improvement.

Four years later abdominal pain returned acutely and an in-stent thrombosis was successfully treated with balloon angioplasty and re-stenting of the SMA.

The patient died one year later from an unrelated cause.

PATIENT 2

An 80-year-old male with nephrosclerosis/ischemic nephropathy and peripheral vascular disease started chronic hemodialysis at the age of 78. Over the next 2 years, investigations for weight loss revealed a calcified abdominal aorta with chronic colonic ischemia and a proximal SMA stenosis. He underwent angiography with stenting of the celiac artery. Following the procedure, he gained weight, and inflammatory parameters improved. Five years after the angioplasty he died as a result of a cerebrovascular accident.

PATIENT 3

A 52-year-old male with diabetic nephropathy, morbid obesity, and heart failure secondary to ischemic heart disease had been treated by hemodialysis for 5 years. He started to complain of postprandial abdominal pain and food aversion, and lost 11 kg within the next 6 months. Gastroscopy was normal, and CTA showed significant SMA and inferior mesenteric artery (IMA) stenosis with calcifications and near complete occlusion of the entire left gastric artery. He underwent angiography and stenting of the SMA. His clinical condition improved markedly and within 3 months he underwent successful living-related kidney transplantation. He died 6 years later from complications of biventricular heart failure after returning to chronic hemodialysis a few months previously.

PATIENT 4

A 60-year-old male with a history of smoking, diabetes mellitus, and severe generalized atherosclerosis had been treated by chronic hemodialysis for 3 years. He then developed abdominal angina, which resulted in a significant weight loss. CTA demonstrated splenic and renal infarcts together with severe thrombotic atherosclerosis of the abdominal aorta and severe SMA and IMA calcifications and stenosis. He underwent angiography

and placement of a stent at the ostium of the SMA. His abdominal pain improved immediately but reappeared 18 months after the first procedure. Repeat CTA showed the patent stent within the SMA, with less than a 50% stenosis immediately distal to the stent. He was treated conservatively and the pain resolved. One year later (2.5 years after the first angioplasty), the patient passed away from sudden death.

PATIENT 5

An 88-year-old female had been treated by chronic hemodialysis for 2 years. Dialysis was complicated by transient neurological ischemic attacks. She later had episodes of abdominal pain and bloody diarrhea caused by right colonic ischemia. Because of continuing abdominal pain, aversion to food, and weight loss she underwent angiography with stenting of the SMA ostium. Five months later she died as a result of the MIA syndrome and a cerebrovascular event.

PATIENT 6

A 60-year-old cachectic female and heavy smoker was known to have a near-complete atherosclerotic occlusion of her infrarenal abdominal aorta and a 50% stenosis of her left main renal artery. She was on anticoagulants because of the anti-phospholipid antibody syndrome. When serum creatinine was 1.2 mg/dl, with creatinine clearance 29 ml/min, abdominal angina was suspected because of aversion to food and a 10 kg weight loss. An magnetic resonance imaging showed a completely calcified infrarenal occlusion of the abdominal aorta and severe narrowing of the celiac artery. She underwent angiography through a transbrachial artery approach. Severe narrowing of the celiac artery was demonstrated at its origin along with moderate SMA stenosis. A stent was placed in the celiac artery. The abdominal pain improved and within the next 6 months she gained 2 kg. At that time the abdominal pain recurred. A repeat transbrachial angiography showed an in-stent occlusion within the celiac trunk, which was treated by balloon angioplasty. Eight months following the procedure she initiated hemodialysis.

In all patients there were no complications related to the procedures, and 30-day mortality was 0%.

DISCUSSION

Mesenteric ischemia among chronic dialysis patients is usually of the non-occlusive type, and is often associated with a dismal patient outcome [1-3,11]. Occlusive mesenteric ischemia has been infrequently described in the chronically dialyzed population. Possible reasons for this may be the chronic nature of the disorder, which is manifested by postprandial abdominal pain (abdominal angina), food aversion, and a gradual weight loss. These symptoms are common in dialysis patients and are often misinterpreted as under-dialysis, or other intra-abdominal pathologies. The condition of occlusive mesenteric ischemia re-

quires a high degree of suspicion. Otherwise, a picture of malnutrition-inflammation-atherosclerosis (MIA) syndrome will develop with a resulting high mortality rate [12].

Only a few reports have described occlusive mesenteric ischemia among dialysis patients. In 1981 three female dialysis patients presented with abdominal angina and weight loss. All three subsequently died, and on autopsy all three patients were found to have severe occlusions of both SMA and IMA [7]. Pre-death diagnosis of occlusive mesenteric disease was not made, and treatment not given. In 2002, another patient, a 73-year-old male on chronic dialysis with chronic abdominal angina and weight loss over several years, was eventually successfully treated with stenting of the celiac artery [8]. Another case was reported in 2007 of a dialysis patient with celiac territory syndrome, which was successfully treated by stenting of the SMA [9]. Recently, a patient with pre-dialysis chronic kidney disease had successful stenting of the SMA artery using intravascular ultrasound without the use of radiocontrast injection [10].

A high level of suspicion is required for an early diagnosis. Correct diagnosis depends on an accurate radiographic assessment and may include sonographic Doppler examination of the major abdominal arteries. CTA is considered the gold standard test. However, diagnostic accuracy of CTA is often hampered by the presence of both medial and intimal vascular calcifications – a problem so common in the dialysis population [13]. These calcifications, mainly the medial, are more common and unique among dialysis patients compared with atherosclerotic non-dialysis patients [13]. Thus, CTA may often be inconclusive. Therefore, early abdominal angiography is often necessary, and despite its risks, has the advantage of leading to accurate diagnosis as well as to treatment. A significant clinical manifestation correlates with the involvement of at least two of the three major abdominal arteries supplying the small and large bowel; the celiac, SMA, and IMA.

The options for treatment include surgical revascularization or endovascular angioplasty with stenting of the diseased artery. Based on repeated studies (in non-dialysis cohorts) comparing the endovascular approach to surgery (with respect to primary patency, recurrence, morbidity, and mortality), it seems that endovascular treatment is the preferred choice and should therefore be considered as the initial mode of therapy [14-18].

Our study group included chronic dialysis patients who presented with occlusive mesenteric vascular disease that was amenable to treatment. All the patients were high risk patients for major atherosclerotic disease and all had overt manifestations of arterial occlusive diseases. Not surprisingly, 5/6 patients were heavy smokers. As may occur with a condition that requires a high level of suspicion, the first patient was diagnosed late and after exclusion of other intra-abdominal problems. With the subsequent patients, the diagnosis was made at an earlier stage, clearly a benefit to those involved patients. Two patients underwent a second successful endovascular procedure, 4 years and 6 months after the first angiography.

All patients developed hypoalbuminemia and elevated CRP along with their clinical picture, which all reversed to normal or improved following therapy [Table 2].

Important to note, there were no adverse events or deaths related to the angiographic procedures (follow-up period: 1-6 years).

The study limitation is the relatively small group of patients.

CONCLUSIONS

Chronic dialysis patients may develop occlusive mesenteric disease. The patients are usually elderly, with multiple co-morbidities. They all have evidence of diffuse macro-vascular disease. The diagnosis needs to be anticipated or it can be missed. Heavy intravascular calcifications may reduce the accuracy of CTA, and because of the high dose of contrast dye given, may reduce residual renal function in dialysis patients. Therefore, angiography should be considered as a first line diagnostic option in selected patients. Angioplasty with stenting of the relevant mesenteric vessel appears highly beneficial in resolving symptoms and improving the malnutrition-inflammation-atherosclerosis complex, with a resultant improved patient survival.

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References

1. Ori Y, Chagnac A, Schwartz A, et al. Non-occlusive mesenteric ischemia in chronically dialyzed patients: a disease with multiple risk factors. *Nephron Clin Pract* 2005; 101: c87-c93.
2. Bassilios N, Menoyo V, Berger A, et al. Mesenteric ischemia in haemodialysis patients: a case-control study. *Nephrol Dial Transplant* 2003; 18: 911-17.
3. Zeier M, Wiesel M, Rambauek M, Ritz E. Non-occlusive mesenteric infarction in dialysis patients: the importance of prevention and early intervention. *Nephrol Dial Transplant* 1995; 10: 771-3.
4. Haberer J, Trivedi NN, Kohlwe J, Tierney L. A gut feeling. *N Engl J Med* 2003; 349: 73-8.
5. Gotsman I, Verstandig A. Intravascular stent implantation of the celiac artery in the treatment of chronic mesenteric ischemia. *J Clin Gastroenterol* 2001; 32 (2): 164-6.
6. Sreenarasimhaiah J. Chronic mesenteric ischemia. *Best Pract Res Clin Gastroenterol* 2005; 19 (2): 283-95.
7. Vaz AJ. Abdominal angina in patients receiving long-term hemodialysis. *South Med J* 1981; 74: 175-7.
8. Duclos J, Urquieta MS, Opazo M. Mesenteric angina: infrequent cause of chronic pain in hemodialysis patient. *Rev Med Chil* 2002; 130: 1155-8.
9. Ori Y, Korzets A, Neyman H, et al. Celiac territory ischemic syndrome in a patient on chronic hemodialysis. *Clin Nephrol* 2007; 68 (4): 253-7.
10. Fukuda K, Higashimori A, Yokoi Y. Intravascular ultrasound-guided mesenteric stenting in patients with advanced chronic kidney disease. *Ann Vasc Surg* 2016; 35: 205.e5-205.e8.
11. Li SY, Chen YT, Chen TJ, Tsai LW, Yang WC, Chen TW. Mesenteric ischemia in patients with end-stage renal disease: a nationwide longitudinal study. *Am J Nephrol* 2012; 35: 491-7.
12. Pecoits-Filho R, Lindholm B, Stenvinkel P. The malnutrition, inflammation, and atherosclerosis (MIA) syndrome – the heart of the matter. *Nephrol Dial Transplant* 2002; 17 (suppl 11): 28-31.

13. London GM, Guerin AP, Marchais SJ, Metivier F, Pannier B, Adda H. Arterial media calcification in end-stage renal disease: impact on all-cause and cardiovascular mortality. *Nephrol Dial Transplant* 2003; 18 (9): 1731.
14. Tallarita T, Oderich GS, Gloviczki P, et al. Patient survival after open and endovascular mesenteric revascularization for chronic mesenteric ischemia. *J Vasc Surg* 2013; 57 (3): 747-55.
15. Atkins MD, Kwolek CJ, LaMuraglia GM, Brewster DC, Chung TK, Cambria RP. Surgical revascularization versus endovascular therapy for chronic mesenteric ischemia: A comparative experience. *J Vasc Surg* 2007; 45: 1162-71.
16. Barret M, Martineau C, Rahmi G, et al. Chronic mesenteric ischemia: a rare cause of chronic abdominal pain. *Am J Med* 2015; 128: 1363.e1-e8.
17. Pecoraro F, Rancic Z, Lachat M, et al. Chronic mesenteric ischemia: critical review and guidelines for management. *Ann Vas Surg* 2013; 27: 113-22.
18. Cai W, Li X, Shu C, et al. Comparison of clinical outcomes of endovascular versus open revascularization for chronic mesenteric ischemia: a meta-analysis. *Ann Vas Surg* 2015; 29: 934-40.

Capsule

Brakes off cyclin drives memory

Cyclin-dependent kinases 4 and 6 (CDK4/6) are enzymes that stimulate cell proliferation. CDK4/6 inhibitor (CDK4/6i) drugs block the signals that instruct tumor cells to divide and have been approved to treat a subset of breast cancers. Heckler et al. and Lelliott et al. found that CDK4/6i can also promote the formation of immune memory to help fight tumors. Short-term treatment of cancer cells with CDK4/6i pushed activated CD8+ T lymphocytes along a memory

cell trajectory, which promoted long-term tumor immunity in mice. These findings may guide the design of human clinical trials using CDK4/6i as a cancer pretreatment to kick-start the immune response before the addition of immunotherapeutic agents.

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Capsule

Defenses against SARS-CoV-2 variants

A key defense against the COVID-19 pandemic is neutralizing antibodies against the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus elicited by natural infection or vaccination. Recent emerging viral variants have raised concern because of their potential to escape antibody neutralization. Wang et al. identified four antibodies from early-outbreak convalescent donors that are potent against 23 variants, including variants of concern,

and characterized their binding to the spike protein of SARS-CoV-2. Yuan et al. examined the impact of emerging mutations in the receptor-binding domain of the spike protein on binding to the host receptor ACE2 and to a range of antibodies. These studies may be helpful for developing more broadly effective vaccines and therapeutic antibodies.

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Capsule

Spying on microbial communities, cell by cell

Within any community of organisms, gene expression is heterogeneous, which can manifest in genetically identical individuals having a different phenotype. One has to look at individuals in context and analyze patterns in both space and time to see the full picture. Aiming to fill a gap in current methods, Dar et al. developed a transcriptome-imaging method named parallel sequential fluorescence in situ hybridization (par-seqFISH). They applied this technique to the opportunistic pathogen *Pseudomonas aeruginosa*, focusing on biofilms where growth conditions can change

at microscopic scale. Development of these communities, as revealed by mRNA composition, was followed in space and time. The results revealed a heterogeneous phenotypic landscape, with oxygen availability shaping the metabolism at a spatial scale of microns within a single contiguous biofilm segment. This tool should be applicable to complex microbial communities in the environment and the human microbiome.

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